transcription of the trapped gene and results in a null mutation at the locus. In this application, the claimed invention relates to polynucleotides comprising the disclosed polynucleotide sequences of SEQ ID NOS:9-18 which are trapped genes obtained from human teratocarcinoma cells. The present invention also relates to an *in vitro* process for producing a polynucleotide that encodes nucleotides in SEQ ID NOS:9, 10, 12-14, and 16-18.

II. THE REJECTION UNDER 35 U.S.C. § 101 (UTILITY)

Claims 3 and 5-13 are rejected under 35 U.S.C. § 101 as allegedly lacking patentable utility. In particular claims 3 and 5-13 were rejected because the claimed invention allegedly is not supported by either specific and/or substantial or well-established utility. Applicants respectfully traverse the rejection on the ground that claims 3 and 5-13 have utility. Specifically, Applicants assert that the identified sequences represent a specific class of genes that is involved in cell differentiation. The usefulness of such genes is well-established in the art.

In their response to the previous office action, Applicants have argued that the genetic loci that are represented by the presently claimed polynucleotides fall within a specific class of genes. These genetic loci encode genetic functions that are not involved in the general survival, *i.e.*, house-keeping functions, of teratocarcinoma cells because one functional allele of these genes is sufficient for cell survival and growth. Thus, these genetic loci and the products encoded by these loci are preselected for possessing functions that are specifically involved in the differentiation and development of such cells.

In the office action of April 23, 2002, the Examiner alleges that Applicants do not specifically identify the specific class of genes to which the claimed polypeptides belong. The Examiner further contends that "merely because a disruption in a genetic allele is not lethal is not necessarily evidence that a gene is not involved in 'general survival' or is not a housekeeping gene". Further, the Examiner contends that for the proper function of many genes, one functional copy of the gene is sufficient.

In response, Applicants point out that the insertion of the trapping vector into a gene will interrupt the proper function of that copy of the gene. If the gene is required for cell viability, this reduction of gene activity by 50% will in most cases result in a decrease of cell viability. Thus, in a population of cells exposed to the gene trapping vectors of the invention, the percentage of cells that can be identified as suffering from a 50% reduction in gene

activity of a gene required for cell viability is disproportionally lower than the actual percentage of genes in the genome that are essential for cell viability, because of their reduced viability. On the other hand, in the same population, the percentage of cells with an insertion of the gene trap vector in a gene that is not required for cell viability will be higher than the percentage of genes in the genome that are not required for cell viability. As the sequences of the invention are derived from the cells with insertions of the gene trap vector, the number of identified genes that are not required for cell viability will be higher compared to the number of genes in the genome that are not required for cell viability. The gene-trapping method of the present invention therefore pre-selects a class of genes that is not involved in cell viability but is involved in cell differentiation and development. Thus, the gene trap method enriches a class of genes that is involved in cell differentiation and development.

Further the gene trap method identifies genes that would not have been identified by conventional forward genetics. By conventional forward genetics, the cells are mutated and selected for reduced cell viability. Subsequently, the mutation is genetically mapped using the reduction in cell viability as a marker. Based on the genetic map position, the gene is cloned. Without a phenotype, the mutation cannot be genetically mapped and the associated gene cannot be cloned. The gene trap method, in contrast, pre-selects for a class of genes that is not required for cell viability, and effectively narrows the scope of the identification process.

Further, the sequences set forth in SEQ ID NOS: 9-18 represent genetic sequences that play a role in late stages of stem cell differentiation and development. Accordingly, the utility of these sequences are not general and are not shared by any random pieces of genomic DNA. Not every gene in the genome necessarily provide this specific utility of the polynucleotides of the invention. Applicants submit that these genetic loci as represented by the presently claimed polynucleotides have substantial utility because they provide useful information regarding gene expression in teratocarcinoma cells which mimics gene expression during the late stages of stem cell differentiation and development.

Further, the Examiner contends that the claimed invention lacks utility because the specification fails to disclose evidence to support the argument that the sequences of the invention can be used to study development and cell differentiation. The Examiner contends that the claimed invention lacks utility because the Applicants do not specifically identify

sequences which are associated with disorders involving development and cell differentiation. Applicants respectfully disagree.

In response, Applicants respectfully point out that the Utility Guidelines provide that, in evaluating evidence related to utility, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed and whether the asserted utility appears to contravene established scientific principles and beliefs. For the claimed utility to be credible, the invention must be "believable based on the record or the nature of the invention" (M.P.E.P. 2107.02(III)(A). Applicants assert that because of the nature of the invention and for the reasons set forth above, the sequences of the invention are pre-selected for sequences representing genes that are involved in the differentiation of teratocarcinoma cells. Such genes can be used for the development of therapeutic methods to treat diseases involving abnormal cell differentiation.

The Examiner further contends that "a 'use' to do further research (*e.g.*, to identify a gene which is involved in development, differentiation, signal transduction, etc.) is not considered a specific, substantial, and credible utility.

In response, Applicants respectfully point out that the pre-selected class of genes facilitates the identification of important regulators of cell differentiation. For example, the sequences identified by the gene trap method have utility when assembled on a micro-array. When the micro-array is hybridized with RNA from teratocarcinoma cells of different differentiation stages, genes that are involved in the differentiation of this type of cells are identified. Using a micro-array with the class of genes that is pre-selected for genes involved in differentiation and development as opposed to cell viability reduces the number of genes that need to be screened compared to a micro-array of genes randomly picked from a genome sequence database.

Further, the sequences of the invention provide the skilled artisan with probes to isolate the full length cDNA of the genes represented by the sequences of the invention without undue experimentation. The full length cDNAs can be obtained by cDNA library screening with the sequences of the invention. Full length cDNAs can also be obtained by 3' or 5' RACE. The sequences of those genes are useful for identifying polymorphisms in coding regions and associating those polymorphisms with disorders. For the reasons set forth above, those genes are pre-selected for genes involved in cell differentiation; they can,

therefore, be used for developing therapies for disorders involving abnormal cell differentiation.

Since the sequences of the invention are clearly stated as being useful for elucidating gene expression during cell differentiation and for developing therapies for disorders and diseases involving abnormal cell differentiation and for the other utilities discussed in the specification, Applicants submit such sequences satisfy the requirements for patentability under 35 U.S.C. § 101. Applicants therefore respectfully request that the rejection of claims 3 and 5-13 under 35 U.S.C. § 101 be withdrawn.

Further, Applicants invite the Examiner to consider the following argument. The sequences recited in claim 3 and 5-13 are expressed in the cells via the insertion of the gene trap vector. As the cells are still viable despite the expression of those sequences, the expression of those sequences is not cytotoxic to the cells. Therefore, the sequences recited in claim 3 and 5-13 are useful for the expression in cells. Expression of these sequences in a cell is useful to determine, *e.g.*, the modification of signal transduction pathways, modifications in cell differentiation, and modifications in the cell division cycle.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, (WRITTEN DESCRIPTION)

Claims 3 and 10-13 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification. Particularly, the claims were rejected for using open language such that the claimed polynucleotides may comprise sequences not disclosed by the specification. Applicants traverse this rejection on the ground that claim 3 and 10-13 are fully supported by the specification and claims as originally filed. Specifically, Applicants assert that the skilled artisan can distinguish the claimed sequences from other sequences and can identify many of the species that the claims encompass. Thus, claims 3 and 10-13 meet the standard for the written description requirement under 35 U.S.C. § 112, first paragraph.

According to 35 U.S.C. § 112, first paragraph, an applicant must convey with reasonably clarity to those skilled in the art that the applicant was in possession of the invention. *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An adequate description of a chemical genus requires a precise definition by *structure*, *formula*, *chemical name* or *physical properties* sufficient to distinguish the genus from other materials. *Fiers v.*

Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). The standard for claims involving chemical materials has been explicitly stated by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acid by *structure*, *formula*, *chemical name* or *physical properties* sufficient to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. By virtue of the sequences recited in claims 3 and 10-13, the claimed isolated polynucleotides are fully described by *structure* or by *physical properties*, or both, sufficient to distinguish the claimed isolated polynucleotides from other materials.

Claim 3 recites an isolated polynucleotide that comprises a contiguous stretch of at least about 60 nucleotides of at least one of SEQ ID NOS:9, 12-14, and 16-18. Thus, one of skill in the art can readily distinguish the isolated polynucleotides of claim 3 from other materials by the description provided in claim 3. Whether a particular nucleic acid sequence comprises 60 contiguous nucleotides of at least one of SEQ ID NOS:9, 12-14, and 16-18 can be determined by the skilled artisan by sequence analysis and/or hybridization of the nucleic acids under stringent conditions. Further, claim 13 recites an isolated polynucleotide capable of hybridizing to a polynucleotide of Claim 3, 10 or 11. New Claim 13 describes a genus of polynucleotides by a *physical property* that readily distinguishes the claimed polynucleotides from other materials. In particular, those polynucleotides with the *physical property* of being capable of hybridizing to a polynucleotide of Claim 3, 10 or 11 are within the genus of Claim 13. Other chemical materials that lack this *physical property* are not within the genus. One of skill in the art can readily distinguish the polynucleotides of Claim 13 from other materials. New Claim 13 thus meets the written description requirement.

The Examiner contends that the written description standard is not met because the claimed sequences may comprise repetitive sequences or entire open reading frames that are not described in the application. Applicants respectfully disagree.

Merely because the sequences may contain sequences in addition to at least about 60 contiguous nucleotides of at least one of SEQ ID NOS:9, 12-14, and 16-18, the

claims should not be rejected for lack of written description. Here, the new aspect of the claimed isolated polynucleotides is the stretch of at least about 60 contiguous nucleotides of at least one of SEQ ID NOS:9, 12-14, and 16-18, which is unambiguously described in the application by virtue of the sequence listing.

Applicants respectfully request that the rejections of claims 3 and 10-13 under 35 U.S.C. § 112, first paragraph, be withdrawn.

CONCLUSION

Applicants submit that claims 3 and 5-13 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of claims 3 and 5-13 to issuance is therefore kindly solicited.

In addition to the extension fee, no fees are believed due in connection with this response. Should any additional fees be due, however, the Commissioner is authorized to charge the additional fees to Pennie & Edmonds Deposit Account No. 16-1150.

Respectfully submitted,

Date: October 23, 2002

Laura A. Coruzzi 30,742
Laura A. Coruzzi (Reg. No.)
By Jonathan M. Lindsay (Reg No. 35,203)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Exhibit A
Pending Claims

3. An isolated polynucleotide comprising a contiguous stretch of at least about 60 nucleotides of at least one of SEQ ID NOS:9, 12-14, 16-18.

5. An *in vitro* process for producing a polynucleotide comprising the steps of:

a) obtaining a polynucleotide template encoding a sequence capable of hybridizing to a gene trapped sequence of SEQ ID NOS:9, 10, 12-14, 16-18;

b) combining said template with a synthetic oligonucleotide sequence of about 14 to about 80 bases in length that comprises a contiguous sequence of at least about 12 nucleotides disclosed in one of SEQ ID NOS:9, 10, 12-14, 16-18; and

c) processing the combined oligonucleotide and template preparation such that said oligonucleotide sequence hybridizes to said template in the presence of a DNA polymerase molecule and a sufficient concentration of dNTPs for said oligonucleotide sequence to prime DNA synthesis by said polymerase,

wherein a polynucleotide is produced that encodes at least about 50 contiguous nucleotides first disclosed in one of SEQ ID NOS:9, 10, 12-14, 16-18.

6. The process of Claim 5 wherein said template is mammalian cDNA.

7. The process of Claim 5 wherein said template is mammalian genomic DNA.

8. The process according to Claim 6 wherein said template is of human origin.

9. The process according to Claim 7 wherein said template is of human origin.

10. An isolated polynucleotide comprising a contiguous stretch of at least about 30 nucleotides of at least one of SEQ ID NO:9, 13, 14, 17, or 18.

11. An isolated polynucleotide comprising a contiguous stretch of at least about 40 nucleotides of at least one of SEQ ID NO:9, 12-14, 16-18.

12. An isolated polynucleotide comprising at least one of SEQ ID NOS:9-18.

13. An isolated polynucleotide of at least about 40 nucleotides capable of hybridizing to a polynucleotide consisting of a sequence selected from the group consisting of SEQ ID NO:9, 12, 13, 14, 16, 17, and 18, under high stringency conditions, said conditions comprising incubating at 65°C in 0.5M $NaHP0_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA and washing at 68°C in 0.1xSSC and 0.1% SDS.